

In re: Application of Ekwuribe et al.
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At page 12, line 16, please insert the term -- (~~SEQ ID NO:1~~) -- after the term "CHOLESTEROL MET-ENKEPHALIN-LYS".

At page 12, line 29, please insert the term -- (~~SEQ ID NO:1~~) -- after the term "PALMITATE MET-ENKEPHALIN-LYS".

At page 12, line 44, please insert the term -- (~~SEQ ID NO:2~~) -- after the term "DI-PALMITATE-TEG MET-ENKEPHALIN-LYS".

At page 13, line 14, please insert the term -- (~~SEQ ID NO:50~~) -- after the term "leu-enkephalin lysine".

At page 13, lines 14-15, please insert the term -- (~~SEQ ID NO:49~~) -- after the term "met-enkephalin lysine".

At page 13, line 20, please insert the term -- (~~SEQ ID NO:1~~) -- after the term "Enkephalin".

At page 13, line 21, please insert the term -- (~~SEQ ID NO:1~~) -- after the term "Enkephalin".

At page 17, line 5, please insert the term -- (~~SEQ ID NO:1~~) -- after the term "cetyl-PEG2-enkephalin-lys".

At page 17, line 6, please insert the term -- (~~SEQ ID NO:48~~) -- after the term "unconjugated enkephalin".

At page 17, line 7, please insert the term -- (~~SEQ ID NO:1~~) -- after the term "cetyl-PEG3-enkephalin".

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At page 17, line 8, please insert the term -- (SEQ ID NO:47) -- after the term "unconjugated enkephalin".

At page 17, line 9, please insert the term -- (SEQ ID NO:1) -- after the term "palmitate-PEG3-Enk".

At page 17, line 10, please insert the term -- (SEQ ID NO:47) -- after the term "unconjugated enkephalin".

At page 17, lines 13-14, please insert the term -- (SEQ ID NO:1) -- after the term "cetyl-PEG₂-enkephalin".

At page 17, line 15, please insert the term -- (SEQ ID NO:1) -- after the term "cetyl-PEG₂-enkephalin".

At page 18, line 12, please replace the term "lipophilic" (second occurrence) with the term -- hydrophilic --.

At page 20, line 2, please replace the term "an" (second occurrence) with the term --a--.

(20) At page 20, line 4, please replace the term "peptide" with the term -- drug --.

At page 20, line 26, please insert the term -- (SEQ ID NO:1) -- after the term "Enkephalin".

At page 20, line 27, please insert the term -- (SEQ ID NO:1) -- after the term "Enkephalin".

At page 21, line 4, please insert the term -- (SEQ ID NO:3) -- after the term

"Enkephalin".

At page 21, line 6, please insert the term -- (SEQ ID NO:3) -- after the term "Enkephalin".

At page 24, line 13, please insert the term --is-- after the term "which".

At page 24, line 14, please replace the term "are" with the term --is--.

Please replace the paragraph beginning at page 24, line 28 with the following paragraph:

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--In another aspect, the therapeutic peptide of the amphiphilic drug-oligomer conjugates are as described in United States Patent 5,641,861, which is incorporated herein by reference, so long as any of such peptides contains a lysine residue. Exemplary peptides described therein include: Ac-Phe-Arg-Trp-Trp-Tyr-Lys—NH₂ (SEQ ID NO:4); Ac-Arg-Trp-Ile-Gly-Trp-Lys—NH₂ (SEQ ID NO:5); Trp-Trp-Pro-Lys-His-Xaa—NH₂ (SEQ ID NO:6), where Xaa can be any one of the twenty naturally occurring amino acids, or Trp-Trp-Pro-Xaa—NH₂ (SEQ ID NO:7), where Xaa is Lys or Arg; Tyr-Pro-Phe-Gly-Phe-Xaa—NH₂ (SEQ ID NO:8), wherein Xaa can be any one of the twenty naturally occurring amino acids; (D)Ile-(D)Met-(D)Ser-(D)Trp-(D)Trp-Gly_n-Xaa—NH₂ (SEQ ID NO:9), wherein Xaa is Gly or the D-form of a naturally-occurring amino acid and n is 0 or 1, peptides of this formula can be hexapeptides when Gly is absent (n is 0) and heptapeptides when Gly is present (n is 1); (D)Ile-(D)Met-(D)Thr-(D)Trp-Gly-Xaa—NH₂ (SEQ ID NO:10), wherein Xaa is Gly or the D-form of a naturally-occurring amino acid; Tyr-A1-B2-C3—NH₂ (SEQ ID NO:11), wherein A1 is (D)Nve or (D)Nle, B2 is Gly, Phe, or Trp, and C3 is Trp or Nap; Pm and red {Me_xH_yN-Tyr-(NMe)_z-Tyr-Xaa_z—NH₂} (SEQ ID NO:12), wherein x and y independently are 0, 1, or 2 and z is 0 or 1, and wherein Xaa is Phe, D-Phe, or NHBzl; Trp-Trp-Pro-D4-His_z-Xaa_z-NH₂ (SEQ ID NO:13), wherein z is 0 or 1, D4 is Lys or Arg and Xaa is any one of the naturally-occurring amino acids.--

Please replace the paragraph beginning at page 25, line 12 with the following paragraph:

63 --In still another aspect, the therapeutic peptide of the amphiphilic drug-oligomer conjugates are as described in United States Patent 5,602,099, which is incorporated herein by reference. with the proviso that the conjugation can occur only where there is a free carboxyl or free N-terminal. Exemplary peptides include: H-Tyr-Tic-Phe-Phe-OH (SEQ ID NO:14); H-Tyr-Tic-Phe-Phe-NH₂ (SEQ ID NO:15); Tyr(NaMe)-Tic-Phe-Phe-OH (SEQ ID NO:16); Tyr(NaCpm)-Tic-Phe-Phe-OH (SEQ ID NO:17); Tyr(NaHex)-Tic-Phe-Phe-OH (SEQ ID NO:18); Tyr(NaEt₂)-Tic-Phe-Phe-OH (SEQ ID NO:19); H-Dmt-Tic-Phe-Phe-OH (SEQ ID NO:20); H-Dmt-Tic-Phe-Phe-NH₂ (SEQ ID NO:21); H-Tyr(3-F)-Tic-Phe-Phe-OH (SEQ ID NO:22); H-Tyr(3-Cl)-Tic-Phe-Phe-OH (SEQ ID NO:23); H-Tyr(3-Br)-Tic-Phe-Phe-OH (SEQ ID NO:24); H-Dmt-TicΨ[CH₂—NH]Phe-Phe-OH (SEQ ID NO:25); H-Dmt-TicΨ[CH₂—NH]Phe-Phe-NH₂ (SEQ ID NO:26); H-Tyr-TicΨ[CH₂—NCH₃]Phe-Phe-OH (SEQ ID NO:27); H-Tyr-TicΨ[CH₂—NH]Hfe-Phe-OH (SEQ ID NO:28); Tyr(NMe)-TicΨ[CH₂—NH]Hfe-Phe-OH (SEQ ID NO:29); H-Tyr-Tic-Phg-Phe-OH (SEQ ID NO:30); H-Tyr-Tic-Trp-Phe-OH (SEQ ID NO:31); H-Tyr-Tic-Trp-Phe-NH₂ (SEQ ID NO:32); H-Tyr-Tic-His-Phe-OH (SEQ ID NO:33); H-Tyr-Tic-2-Nal-Phe-OH (SEQ ID NO:34); H-Tyr-Tic-Atc-Phe-OH (SEQ ID NO:35); H-Tyr-Tic-Phe-Phe(pNO₂)-OH (SEQ ID NO:36); H-Tyr-Tic-Trp-Phe(pNO₂)-OH (SEQ ID NO:37); H-Tyr-Tic-Phe-Trp-NH₂ (SEQ ID NO:38); H-Tyr-Tic-Phe-Phe-Val-Val-Gly-NH₂ (SEQ ID NO:39); H-Tyr-Tic-Phe-Phe-Tyr-Pro-Ser-NH₂ (SEQ ID NO:40); H-Tyr-Tic-Trp-Phe-Tyr-Pro-Ser-NH₂ (SEQ ID NO:41); H-Tyr-Tic-Trp-Phe (pNO₂) -Tyr-Pro-Ser-NH₂ (SEQ ID NO:42) and H-Tyr-Tic-Phe-Phe-Leu-Nle-Asp-NH₂ (SEQ ID NO:43).--

Please replace the paragraph beginning at page 25, line 27 with the following paragraph:

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--Abbreviations in the aforementioned peptides of U.S. Patent 5,602,099 may be interpreted as follows: Aib= α -aminoisobutyric acid; Atc=2-aminotetralin-2-carboxylic acid; Boc=tert-butoxycarbonyl; Cpm=cyclopropylmethyl; DCC=dicyclohexyl-carbodiimide; DIEA=diisopropylethylamine; Dmt=2,6-dimethyltyrosine; Et=ethyl; Hex=hexyl; Hfe=homophenylalanine; HOBt=1-hydroxybenzotriazole; MVD=mouse vas deferens; 1-Nal=3-(1'-naphthyl)alanine; 2-Nal=3-(2'-naphthyl)alanine; Phe(pNO₂)=4-nitrophenylalanine; Phg=phenylglycine; Tic=1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; TIP=H-Tyr-Tic-Phe-OH (SEQ ID NO:44); TIP-NH₂=H-Tyr-Tic-Phe-NH₂ (SEQ ID NO:45); TIP(Ψ)=H-Tyr-Tic Ψ [CH₂-NH]Phe-OH (SEQ ID NO:46); TIPP=H-Tyr-Tic-Phe-Phe-OH (SEQ ID NO:14); TIPP-NH₂=H-Tyr-Tic-Phe-Phe-NH₂ (SEQ ID NO:15); TIPP(Ψ)=H-Tyr-Tic Ψ [CH₂-NH]Phe-Phe-OH (SEQ ID NO:47); Tyr(3-Br)=3-bromotyrosine; Tyr(3-Cl)=3-chlorotyrosine; Tyr(3-F)=3-fluorotyrosine; and Tyr(N α Me)=N α -methyltyrosine.--

At page 26, lines 19-20, please insert the term -- (SEQ ID NO:48) -- after the term "[Met⁵]Enkephalin (Tyr-Gly-Gly-Phe-Met)".

At page 27, line 18, please replace the term "peptidominetic" with the term -- peptidomimetic --

At page 27, line 30, please insert the term -- the peptide's -- after the term "increase".

At page 39, line 22, please replace the term "0 °C" with the term -- 0°C --.

At page 40, line 1, please replace the term "25 °C" with the term -- 25°C --.

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At page 40, line 6, please replace the term "MET-ENKEPHLIN" with the term -- MET-ENKEPHALIN--.

At page 40, line 14, please insert the term -- (SEQ ID NO:48) -- after the term "met-enkephalin".

At page 40, lines 15 and 17, please replace the term "10 °C" with the term -- 10°C --.

At page 40, lines 20, please replace the term "3.1" with the term -- 3:1. --.

At page 41, lines 1 and 4, please replace the term "10 °C" with the term -- 10°C --.

At page 41, line 19, please replace the term "25 °C" with the term -- 25°C --.

At page 41, lines 24-25, please insert the term -- (SEQ ID NO:51) -- after the term "BOC-LEU...ENK...LYS-OH".

At page 42, line 1, please insert the term -- (SEQ ID NO:51) -- after the term "Boc-Leu...enk...Lys-OH".

At page 42, line 2, please replace the term "10 °C" with the term -- 10°C --.

At page 42, line 8, please insert the term -- (SEQ ID NO:51) -- after the term "BOC-LEU...ENK...LYS-OH".

At page 42, line 11, please replace the term "methnol-chloroform" with the term -- methanol-chloroform --.

At page 42, line 15, please insert the term -- (SEQ ID NO:52) -- after the term "LEU...ENK".

At page 42, line 16, please insert the term -- (SEQ ID NO:52) -- after the term "Derivatized BOC-LEU...ENK...LYS-OH".

At page 43, line 2, please replace the term "0.1% trifluoracetic acid" with the term -- 0.1% trifluoroacetic acid --.

At page 43, line 8, please replace the term "<20°C" with the term -- <20°C --.

At page 43, line 19, please replace the term "5 °C" with the term -- 5°C --.

At page 43, line 19, please replace the term "15 °C" with the term -- 15°C --.

At page 43, line 21, please replace the term "5 °C" with the term -- 5°C --.

At page 44, line 5, please insert the term -- (SEQ ID NO:49) -- after the term "MET ENKEPHALIN-LYS".

At page 44, line 7, please insert the term -- (SEQ ID NO:49) -- after the term "Met enkephalin-lys".

At page 44, line 13, please replace the term "37 °C" with the term -- 37°C --.

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At page 44, line 15, please replace the term "60ug/mL" with the term -- 60 µg/mL --.

At page 44, lines 15 and 16, please replace the term "200 uL" with the term -- 200 µL --.

At page 44, line 21, please insert the term -- (SEQ ID NO:1) -- after the term "cetyl-PEG₂-enkephalin".

At page 44, line 22, please insert the term -- (SEQ ID NO:49) -- after the term "met-enkephalin-lys".

At page 44, line 22, please insert the term -- (SEQ ID NO:1) -- after the term "cetyl-PEG₃-enkephalin".

At page 45, line 1, please insert the term -- (SEQ ID NO:49) -- after the term "met-enkephalin-lysine".

At page 45, line 1, please insert the term -- (SEQ ID NO:1) -- after the term "palmitate-PEG₃-enk".

At page 45, line 2, please replace the term "met-enkephalin-enk" with the term -- met-enkephalin-lys (SEQ ID NO:49) --.

At page 45, lines 7 and 17, please insert the term -- (SEQ ID NO:1) -- after the term "cetyl-PEG₂-enkephalin".

At page 45, line 8, please replace the term "monutés" with the term -- minutes --.

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At page 45, lines 22 and 23, please insert the term -- (SEQ ID NO:1) -- after the term "cetyl enkephalin".

At page 45, line 24, please insert the term -- (SEQ ID NO:49) -- after the term "enkephalin".

At page 46, line 8, please insert the term -- (SEQ ID NO:49) -- after the term "Met-enkephalin-lys".

At page 46, line 8, please insert the term -- (SEQ ID NO:1) -- after the term "met-enkephalin-lys derivatives".

At page 46, line 10, please insert the term -- (SEQ ID NO:1) -- after the term "cetyl-enkephalin".

At page 46, lines 13 and 14, please insert the term -- (SEQ ID NO:1) -- after the term "cetyl-PEG₂-enkephalin".

At page 46, line 15, please insert the term -- (SEQ ID NO:1) -- after the term "cetyl-enkephalin".

At page 46, line 27, please insert the term -- (SEQ ID NO:49) -- after the term "enkephalin".

At page 47, table, column 1, please insert the term -- (SEQ ID NO:49) -- after the term "Enkephalin"; and insert the term -- (SEQ ID NO:1) -- after each of the terms "Cetyl-PEG-ENK", "DHA-PEG-ENK", "Cholesterol-PEG-ENK", and "Linolenic-PEG-ENK".

At page 48, line 3, please replace the term "-30⁰C" with the term -- -30°C --.